REMARKS

Claims 1-23 and 29-70 are pending in the present application. Claims 7, 14-15, 22, 29-30, 37, 43-44, 48-57, 58, and 68-70 are withdrawn from further consideration as being drawn to non-elected inventions/species. Claims 1-6, 8-13, 16-21, 23, 31-36, 38-42, 45-47, and 59-67 are currently under consideration. By virtue of this response, claims 10 and 40 are amended, and claims 29, 30, 48-58, and 68-70 are cancelled. Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented.

With respect to all claim amendments and cancellations, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is entitled **"VERSION WITH MARKINGS TO SHOW CHANGES MADE."**

Formal drawings

The Examiner has objected to drawings under 37 CFR 1.84, alleging margins for Figures 1, 5, 7-9 are not acceptable, and numbers, letters and reference characters in Figures 2, 6, and 10 are not at least 0.32 cm in height.

New drawings (Figures 1-11) are submitted with this amendment. Applicant respectfully requests withdrawal of this objection.

Color photographs and color drawings

Applicants submit Figures 1-5, and 8-9 (3 in color and 1 in black and white for each Figure) as color drawings. The specification has been amended to describe the presence of

drawings executed in color. A Petition to Accept Photographic Drawings Under 37 C.F.R. § 1.84(b) accompanied with appropriate fee set forth in 37 CFR 1.17(h) are filed with this Amendment. Applicants respectfully request that these color drawings be accepted.

Withdrawal of previous rejections under 35 U.S.C. § 112, first paragraph and second paragraph

Applicants acknowledge with appreciation that the Examiner has withdrawn rejections of claims 10 and 40 made in Office Action of 1/15/02 under the first paragraph of 35 U.S.C. § 112 and the second paragraph of 35 U.S.C. § 112 as they pertain to ASC, ESC, ROG, NODD, BR516, and NEP cells; and the Examiner has withdrawn rejections of claims 10 and 40 under the first paragraph of 35 U.S.C. § 112 as they pertain to RL-65 (ATCC NO. CRL-10345) in view of Applicants' assurances of maintenance and availability of the deposited cell line.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 10 and 40 under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner contends that the specification provides only a teaching sufficient to obtain similar epithelial cell lines, but not the specific cell lines of the claims; and absent a deposit and appropriate assurances, the rejection must be maintained.

Without acquiescence to the rejection and in the interest of expediting prosecution, claims 10 and 40 have been amended to delete "BUD" and "RED" cells. Thus, this rejection is moot. Applicants respectfully request withdrawal of this rejection.

Rejections under 35 U.S.C. § 103(a)

Claims 1-6, 8-13, 16-21, 23, 31-36, 38-42, and 45-47 stand rejected under 35 U.S.C. §103(a) as being allegedly obvious over U.S. Patent No. 5,932,704 ('704 patent), in view of U.S. Patent No. 5,714,385 ('385 patent). Specifically, the Examiner alleges that the Applicants argue that neither reference individually teaches or suggests the claimed invention and states that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. The Examiner further contends that the '704 patent teaches a method of immunization to produce a population of monoclonal antibodies, as well as a method of generating a plurality of monoclonal antibodies, said method employing viable whole cells and antigens in a "native configuration" and the '385 patent provides the motivation for using ASC or ESC cultured in serum-free media, i.e., enhanced viability and proliferation. The Examiner concludes that the combined references teach the invention of the instant claims.

Applicants respectfully traverse this rejection.

Applicants respectfully note that Applicants, in the previous response, did in fact address the issue of the combination of references by arguing that neither reference provides any motivation to combine reference teachings. Absent a motivation to combine, there is no *prima facie* case of obviousness and the rejection may be properly withdrawn on that ground.[1]

As a basis for maintaining this obviousness rejection, the Examiner states his position with respect to the teachings of the '704 patent as allegedly teaching "a method of immunization to produce a population of monoclonal antibodies, as well a method of generating a plurality of monoclonal antibodies, said method employing viable whole cells and antigens in a 'native configuration'". Applicants respectfully note that the '704 patent does not teach or suggest a method of producing or generating a population of monoclonal antibodies, as well as a method of

[1] Applicants further note that there is nothing improper in examining and characterizing each reference individually in the context of obviousness, where it must be determined that (a) there is a motivation to combine; and (b) the combination must teach or suggest all claim limitations.

producing or generating a plurality of monoclonal antibodies using viable whole cells and antigens in a "native configuration", as stated by the Examiner. Instead, the '704 patent only teaches a method of producing or generating antibodies capable binding to a subunit of human GM-CSF receptor using cells expressing high levels of this known, specific receptor. Column 3, lines 32, 35-38; and column 4, lines 5-8. Accordingly, the '704 patent teaches a method of generating one class of antibodies that bind to a known antigen which is expressed at high levels on the cells used as immunogen as opposed to a population of antibodies directed to a spectrum of antigens. In contrast, the present invention teaches a method of producing or generating a population of monoclonal antibodies that bind to cell surface antigens representative of a specific cell type (not a specific antigen). In addition, the '704 patent does not teach or suggest immunization with a plurality of viable and intact cells under conditions that preserve the native configuration of surface antigens on said cells as claimed in the present invention. The '704 patent only teaches that the antibody is preferably generated to a native GM-CSF receptor. Column 3, lines 14-15. Since the entire disclosure of the '704 patent is directed to generating antibodies to a single antigen, there is no disclosure regarding configuration of any other antigens.

Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. These requirements are summarized in the MPEP (MPEP §2143, and §2143.01 to §2143.03), and are based on well-settled case law: *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); and *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

To establish a *prima facie* case of obviousness, there must be some suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. The '704 patent does not teach or suggest a method to produce or generate a population of monoclonal antibodies using viable and intact cells wherein the surface of the cells are free of serum. The '704 patent only teaches producing or generating antibodies to a subunit of human GM-CSF receptor.

The Examiner relies on the secondary reference (the '385 patent) as allegedly forming the basis for the motivation to combine ("for using ASC or ESC cultured in serum-free media, i.e., enhanced viability and proliferation"). Office Action, page 5. Applicants respectfully disagree. The secondary reference (the '385 patent) is solely directed to using a particular serum-free medium, namely one that contains a first mitogenic agent which is a Rse/Axl receptor activator (e.g., gas6) and a second mitogenic agent (e.g., heregulin), to culture a particular cell type, namely, Schwann cells. Column 4, lines 4-10, and lines 18-21; column 1, lines 5-11; column 19, lines 17-21. There is no indication or suggestion in this reference that the medium formulation (presented as useful for Schwann cells in particular, and no other cells) would generally apply to any other cell type, much less the ones taught in the primary reference.

The '385 patent does not provide the motivation for using human Schwann cells cultured in serum-free medium containing a Rse/Axl receptor activator and a second mitogenic agent as immunogen in the method described in the '704 patent, which is directed to generating antibodies to a subunit of human GM-CSF receptor. The '385 patent does not teach or suggest using human Schwann cells as immunogen and does not connect any growth conditions for Schwann cells to immunogenicity.

The rationale proffered by the Examiner for the alleged motivation, namely that enhanced cellular viability and proliferation, refer to culture conditions using a particular medium formulation for Schwann cells, not to their use as immunogens. Serum-free medium used in the '385 patent is a defined medium containing Rse/Axl receptor activator and a second mitogenic agent for growth/maintenance of Schwann cells while at the same time not supporting fibroblast

growth or survival. Col. 3, line 61; see also Abstract. The entire reference is directed to this end. The "enhanced viability and proliferation" arise not just from serum-free medium per se, but a defined serum-free medium that also contains a Rse/Axl receptor activator and a second mitogenic agent. The reference teaching is clear in this regard. Further, the '385 patent makes no reference to use of Schwann cells as immunogens, or that the growth medium containing Rse/Axl receptor activator and a second mitogenic agent contribute to immunogenicity of Schwann cells.

Applicants respectfully note that a prior art reference must be considered in its entirety, i.e., as a whole. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984); MPEP §2141.02. The Examiner cannot choose a portion from the reference and use it for supporting the obviousness rejection without considering the reference in its entirety. Based on the above, these references provide no motivation to combine reference teachings. Thus, the obviousness rejection may be properly withdrawn on this ground.

Applicants respectfully submit that, even if combined (and Applicants contend that there is no motivation to combine), the combined references cited by the Examiner do not teach or suggest all of the claimed limitations. As discussed above, the '704 patent does not teach or suggest a method to produce or generate a population of monoclonal antibodies that bind to cell surface antigens representative a specific cell type by introducing into the host a plurality of viable and intact cells under conditions which preserve the native configuration of surface antigens on said cells. The '704 patent only teaches generating antibodies that bind to a particular antigen, namely, the subunit of human GM-CSF receptor. There is nothing in this disclosure which even suggests generating a population of antibodies which bind to cell surface antigens representative of a specific cell type. Only a single antigen is disclosed. The '385 patent does not cure these deficiencies. As discussed above, the '385 patent does not teach or suggest use of cells for immunization to produce antibodies that bind to cell surface antigens representative of a specific cell type. The '385 patent only teaches cell culture conditions (a

particular serum-free medium formulation containing two additional components, namely, a Rse/Axl receptor activator and a second mitogenic agent) for enhancing the survival and/or proliferation of Schwann cells. Since the '704 patent and the '385 patent when combined do not teach or suggest all the claimed limitations, the Examiner has not set forth a *prima facie* case for obviousness. Thus, the obviousness rejection may be properly withdrawn on this ground.

To establish a *prima facie* case of obviousness, there must also be a reasonable expectation of success. Since the '704 patent only teaches a method of producing or generating antibodies specific for a receptor by immunizing with cells expressing high levels of the receptor, one skilled in the art would not reasonably expect that it would be successful in producing or generating a population of antibodies that bind to cell surface antigens representative of a specific cell type by substituting the cells used in the '704 patent with cells cultured in serum-free medium taught to be particularly applicable to Schwann cells containing a Rse/Axl receptor activator and a second mitogenic agent as described in the '385 patent. Thus, the obviousness rejection may be properly withdrawn on this ground.

In view of the above, Applicants respectfully request that the rejection of claims 1-6, 8-13, 16-21, 23, 31-36, 38-42, and 45-47 under 35 U.S.C. § 103(a) be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-6, 8-13, 16-21, 23, 31-36, 38-42, 45-47, and 59-67 under 35 U.S.C. § 112, first paragraph for allegedly not containing a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. Specifically, the Examiner contends that the recitation of immunizing "repeatedly," and "under conditions which preserve the native configuration of the surface antigens on the cells in claim 1, 11, 31 and the recitation of a method wherein the "repeated introduction into a mammal a plurality of intact cells are without adjuvant in claims 61, 64, and 67 are not supported by the specification and the claims as originally filed. The Examiner further contends that single

embodiment such as Example 2 is insufficient to support the newly added limitations which would encompass the generic invention of the instant claims.

Applicants respectfully traverse this rejection.

MPEP § 2163.02 provides the test for sufficiency of support in an application is whether the disclosure of the application relied upon reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter. The same section of MPEP also provides that the subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement.

A. Recitation of immunizing "repeatedly", and "under conditions which preserve the native configuration of the surface antigens on the cells" in claims 1, 11, and 31

Applicants respectfully submit that the limitations added are supported by the specification and are conveyed to one skilled in the art. Example 2 in the present application clearly discloses that mice were immunized with BUD or RED cells "without adjuvant, weekly for 10 to 15 weeks" or immunized with cells on nitrocellulose discs surgically implanted intraperitoneally "every 2 weeks for 6 weeks". Although the term "repeatedly" was not used in the specification, the term is reasonably conveyed to one skilled in the art by recitation of two examples. The description clearly allows one skilled in the art to recognize that the inventors were in possession of the invention as claimed. The specification also refers to a typical protocol in which a host animal is inoculated and then "boosted". Page 15, lines 7-8. This is standard procedure in the art and conveys repeated inoculations. Repeated inoculations are routinely used in order to generate antibodies, which is the purpose of these claims. In addition, one skilled in the art would understand that the term "repeatedly" in the field of immunizing a host mammal was conveyed in the specification. Applicants note that, as is well known in patent disclosures, the Examples are not single embodiments but are representative of the present invention. Page 20, lines 9-10. The term "Example" clearly indicates this illustrative purpose. Thus, the repeated immunization without adjuvant disclosed in Example 2 for BUD or RED cells can be extended to all other cells.

With respect to the phrase "preserve the native configuration of the surface antigens on the cells", the specification clear provides support for this limitation. The specification states that "[t]his technique also maximizes the preservation of intact antigens, especially surface antigens, for production of a plurality of monoclonal antibodies that bind to the native antigens of a particular cell type." Page 3, lines 4-10. Applicants fail to understand how a technique that "maximizes the preservation of intact antigens" and generates antibodies that "bind to the native antigens of a particular cell type' is vague. This clearly conveys native configuration of antigens. Applicants respectfully ask the Examiner to provide reasoning as to why this claim limitation is not conveyed by the cited passage. The alleged silence in Example 2 is not support for alleged lack of written description. The Example refers to cells grown on discs being implanted surgically. If anything, this "silence" conveys that the integrity of the antigens are preserved. There is nothing in this entire specification that indicates that configuration of cell antigens is not preserved. The monoclonal antibodies generated according to the method of the present invention preferably bind to antigens exhibiting their native configuration and many of the antibodies generated do not recognize denatured antigens immobilized on a Western blot. Page 36, lines 2-4 (which summarizes Examples). Thus, this limitation is clearly supported by the specification.

B. Recitation of a method of "repeated introduction into a mammal a plurality of intact cells are without adjuvant" in claims 61, 64, and 67

As discussed above, the term "repeated" immunization is supported by the specification and is conveyed to one skilled in the art. With respect to the term "without adjuvant", Example 2 provides support for immunization with BUD or RED cells "without adjuvant". As discussed above, since the Examples are not single embodiments but are representative of the present invention, immunization without adjuvant disclosed in Example for BUD or RED cells can be extended to other cells.

In view of the above, Applicants respectfully request that the rejection of claims 1-6, 8-13, 16-21, 23, 31-36, 38-42, 45-47, and 59-67 under 35 U.S.C. § 112, first paragraph be withdrawn.

Nonelected claims

Applicants respectfully submit that nonelected claims 29, 30, 48-58, and 68-70 are cancelled.

CONCLUSION

Applicant has, by way of the amendments and remarks presented herein, made a sincere effort to overcome rejections and address all issues that were raised in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims are respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 415072000110.

Respectfully submitted,

Dated: December 16, 2002 By: _____

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please insert the paragraph at page 5, beginning at line 2, with the paragraph below:

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawings(s) will be provided by the Office upon request and payment of the necessary fee.

In the Claims:

Please amend claims 10 and 40 as follows:

10. (Twice Amended) The method for immunizing a mammal of claim 1, wherein the cells are selected from the group consisting of adult Schwann cells (ASC), embryonic Schwann cells (ESC), [pancreatic epithelial cells from rat e12 embryonic pancreatic buds (BUD), pancreatic epithelial cells from rat e17 ductal epithelium (RED),] and rat lung bronchiolar epithelial cells (RL-65) (ATCC NO. CRL-10354).

40. (Twice Amended) The method for producing a population of monoclonal antibodies according to claim 31, wherein the cells are selected from the group consisting of adult Schwann cells (ASC), embryonic Schwann cells (ESC), [pancreatic epithelial cells from rat e12 embryonic pancreatic buds (BUD), pancreatic epithelial cells from rat e17 ductal epithelium (RED),] and rat lung bronchiolar epithelial cells (RL-65) (ATCC NO. CRL-10354).

Please cancel claims 29, 30, 48-58, and 68-70.